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(54) Title: VACCINE COMPOSITION COMPRISING LIPOOLIGOSACCHARIDE WITH REDUCED PHASE VARIABILITY

(57) Abstract: The present invention relates to the field of neisserial vaccine compositions, their manufacture, and the use of such compositions in medicine. More particularly it relates to processes of making novel engineered meningococcal strains which are less phase variable in terms of their LOS immunotype, and from which novel LOS subunit or meningococcal outer-membrane vesicle (or bleb) vaccines can be derived.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/095

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 01 09350 A (DALEMANS WILFRIED L J ;SMITHKLINE BEECHAM BIOLOG (BE); THIRY GEORG) 8 February 2001 (2001-02-08) cited in the application</p> <p>abstract page 2, line 1 - line 22 page 17, line 11 - line 25 page 26, line 26 -page 27, line 22 page 31, line 14 - line 22 page 33, line 1 - line 30 example 8</p> <p>---</p> <p>-/--</p>	<p>1-26, 28-31, 34,35, 39,40, 42,43, 49,50,52</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19960 A (WOMENS & CHILDRENS HOSPITAL ;LUMINIS PTY LTD (AU)) 22 March 2001 (2001-03-22) page 14, line 6 - line 28 page 42, line 25 -page 44, line 19 page 55, line 8 - line 31 page 60, line 4 - line 27 ---	1-26, 28-31
Y	JENNINGS M P ET AL: "The genetic basis of the phase variation repertoire of lipopolysaccharide immunotypes in Neisseria meningitidis." MICROBIOLOGY (READING, ENGLAND) ENGLAND NOV 1999, vol. 145 (Pt 11), November 1999 (1999-11), pages 3013-3021, XP002270062 ISSN: 1350-0872 cited in the application abstract page 3017, column 1, last paragraph -page 3018, column 1, paragraph 1; figure 4 page 3019, column 1, paragraph 2 page 3019, column 2, last paragraph -page 3020, column 1, paragraph 1 ---	8,9, 12-17, 21,22, 34,39,49
Y	JENNINGS M P ET AL: "Molecular analysis of a locus for the biosynthesis and phase-variable expression of the lacto-N-tetraose terminal lipopolysaccharides structure in Neisseria meningitidis" MOLECULAR MICROBIOLOGY, BLACKWELL SCIENTIFIC, OXFORD, GB, vol. 18, no. 4, 1995, pages 729-740, XP002084665 ISSN: 0950-382X cited in the application abstract page 733, column 1, paragraph 2 -page 734, column 1 page 736, column 2, last paragraph page 737, column 1, last paragraph -column 2, paragraph 1 --- -/--	29

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DRABICK J J ET AL: "Safety and immunogenicity testing of an intranasal group B meningococcal native outer membrane vesicle vaccine in healthy volunteers"</p> <p>VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 18, no. 1-2, 20 August 1999 (1999-08-20), pages 160-172, XP004178826</p> <p>ISSN: 0264-410X</p> <p>cited in the application abstract</p> <p>page 161, column 2, paragraph 3 -page 162, column 1, paragraph 1</p> <p>---</p>	35, 40, 50
Y	<p>BANERJEE ASESH ET AL: "Identification of the gene (lgtG) encoding the lipooligosaccharide beta chain synthesizing glucosyl transferase from Neisseria gonorrhoeae"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 18, 1 September 1998 (1998-09-01), pages 10872-10877, XP002270063</p> <p>Sept. 1, 1998</p> <p>ISSN: 0027-8424</p> <p>abstract</p> <p>page 10872, column 1, paragraph 2</p> <p>page 10872, column 2, last paragraph -page 10873, column 1, paragraph 1</p> <p>page 10874, column 2, last paragraph -page 10875, column 1, paragraph 1</p> <p>page 10875, column 1, paragraph 4 - paragraph 5</p> <p>page 10877, column 1, paragraph 2</p> <p>---</p>	25, 26
Y	<p>GU X X ET AL: "Preparation, characterization, and immunogenicity of meningococcal lipooligosaccharide-derived oligosaccharide-protein conjugates"</p> <p>INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 61, no. 5, May 1993 (1993-05), pages 1873-1880, XP002102900</p> <p>ISSN: 0019-9567</p> <p>abstract</p> <p>page 1873, column 2, paragraph 1 - paragraph 2</p> <p>page 1876, column 2, paragraph 2 -page 1878, column 2, paragraph 3</p> <p>page 1878, column 2, last paragraph -page 1879, column 1, paragraph 1</p> <p>page 1879, column 1, last paragraph</p> <p>---</p> <p>-/--</p>	32, 33, 37, 38, 42, 43, 47, 48, 52

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT 03/08569

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>RUNE ANDERSEN S ET AL: "Lipopolysaccharide heterogeneity and escape mechanisms of Neisseria meningitidis: possible consequences for vaccine development" MICROBIAL PATHOGENESIS, ACADEMIC PRESS LIMITED, NEW YORK, NY, US, vol. 23, 1997, pages 139-155, XP002108656 ISSN: 0882-4010 abstract page 149, column 1, paragraph 1 page 149, column 2, paragraph 2 page 149, column 2, paragraph 4 -page 150, column 1, paragraph 1</p> <p>----</p>	44, 53
Y	<p>ZAKIROV M M ET AL: "Immunological activity of Neisseria meningitidis lipooligosaccharide incorporated into liposomes" ZHURNAL MIKROBIOLOGII EPIDEMIOLOGII I IMMUNOBIOLOGII, vol. 0, no. 1, 1995, pages 49-53, XP008027121 ISSN: 0372-9311 abstract</p> <p>-----</p>	32, 33, 37, 38, 42, 43, 47, 48, 52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08569

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1-53 relate to a process related to neisserial strains with a modified gene defined by a desirable characteristic or property, namely a phase variable LOS oligosaccharide synthesis gene.

The claims cover all neisserial strains with a modified gene having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such genes. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the genes by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the neisserial strains with a modified lgt gene (see page 4, line 29 - page 5, line 10)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No.

PCT 03/08569

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0109350	A	08-02-2001	AU 6833600 A	19-02-2001
			BR 0012974 A	07-05-2002
			CA 2380840 A1	08-02-2001
			CN 1377415 T	30-10-2002
			CZ 20020403 A3	15-05-2002
			WO 0109350 A2	08-02-2001
			EP 1208214 A2	29-05-2002
			HU 0203056 A2	28-12-2002
			JP 2003506049 T	18-02-2003
			NO 20020506 A	02-04-2002
			TR 200200275 T2	21-05-2002
			TR 200202448 T2	21-01-2003
<hr/>				
WO 0119960	A	22-03-2001	AU 7034900 A	17-04-2001
			BR 0013915 A	19-11-2002
			CA 2384081 A1	22-03-2001
			EP 1214396 A1	19-06-2002
			HU 0202863 A2	28-12-2002
			WO 0119960 A1	22-03-2001
			JP 2003514512 T	22-04-2003
			SK 3472002 A3	08-10-2002
			ZA 200201958 A	10-03-2003
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